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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,058	11/30/2001	David W. Threadgill	421/34/2	6701

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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,058	THREADGILL ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27 and 46-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 46-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The present application's claim to benefit of the provisional application, 60/250,706 filed 12/01/2000 is granted.

Election/Restrictions

Applicant's election of Group I, claims 1-27 and 46-53 in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10, 15, 19-27, and 46-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Diehl et al, PNAS 1997.

Diehl et al. teach a method for identifying multiple genetic loci for example, *Col2a1, Col1a1* and *Col3a1*(page 5235) that modulate the phenotype of facial clefting in mice. Diehl et al have performed a genome-wide search for loci contributing to susceptibility to teratogen-induced facial clefting in the mouse. AXB and BXA recombinant inbred(RI) lines derived from crosses between A/J and C57BL6/J strains were supplied by M. Nesbitt and the mice were then

bred by intercrossing recombinant inbred lines and maintained in a colony at the University of Michigan(page 5232) as a renewable population of genetically diverse individuals. The reference teaches this study for identifying a genetic locus in the diploid mouse system wherein the inbred lines of the renewable population of genetically diverse individuals comprise less than about 100 strains, in one instance a BXD set of 26 RI lines is used(page 5234). Experiments were also performed using the AXB and BXA RI strains to evaluate both spontaneous and teratogen-induced clefting resulting in both visual and physiological phenotypes. The reference uses the extensive data on teratogen-induced clefting in the AXB and BXA RI lines collected previously with a genome wide collection of marker typings for these RI lines to study the effects of genetic polymorphisms segregating in the renewable population(page 5232, left column). Diehl et al. teach the resulting molecular phenotype of their mouse mutants with clefting phenotypes to include for example, eight collagen genes including an altered expression of one, *Col3a1*, which is normally expressed in the embryonic palate. The reference also teaches the method for identifying multiple genetic loci further comprising identifying two or more genetic loci that modulate the phenotype of clefting as seen on the reference's page 5235 in their explanation that in addition to *Col3a1*, two other genetic factors, *Col1a1* and a cyclic nucleotide phosphodiesterase gene are located on the same chromosome and are thought to together, be possibly relevant to the role of cAMP in the etiology of cleft palate abnormalities(page 5235). Additionally, the reference teaches the implication of the tenascin C gene, an extracellular matrix protein, and several cell-signaling molecules which have been previously implicated in clefting. Diehl et al. further teach the modulation of the clefting phenotype by a non-genetic factor that is a drug exposure and an interaction between two or more non-genetic factors that are drug

exposures. The reference reports the findings of a genome-wide search for susceptibility genes for teratogen-induced clefting in the AXB and BXA set of recombinant inbred mouse strains, as they compare the results and the interaction between phenytoin(which induces cleft lip) and 6-aminonicotitinamide(which indices cleft palate) and the cleft palate phenotype(abstract and page 5231). The reference also teaches the method of a non-genetic factors ability to modulate the clefting phenotype wherein the phenotype is modulated by environmental, non-genetic factors such as a fetus' exposure in utero to ethanol, trimethadione, aminopterin and retinoic acid(page 5231). Included then in these findings are the reference's teachings of the identification of an interaction among two or more non-genetic factors(both environmental and drug-like) and a genetic locus. Furthermore, as stated previously, this same identification was made among multiple genetic loci discovered in this study in addition to those gene mutations that are well known in the art that the present reference reiterates, such as *Msx1*, several *Hox* genes, retinoic acid receptor alpha locus etc,(page 5231).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Diehl et al. in view of Dindzans et al.(J. of Immunology, 1986).

Diehl et al. teach a method for identifying multiple genetic loci for example, *Col2a1*, *Col1a1* and *Col3a1*(page 5235) that modulate the phenotype of facial clefting in mice. Diehl et

al have performed a genome-wide search for loci contributing to susceptibility to teratogen-induced facial clefting in the mouse. AXB and BXA recombinant inbred(RI) lines derived from crosses between A/J and C57BL6/J strains were supplied by M. Nesbitt and the mice were then bred by intercrossing recombinant inbred lines and maintained in a colony at the University of Michigan(page 5232) as a renewable population of genetically diverse individuals. The reference teaches this study for identifying a genetic locus in the diploid mouse system wherein the inbred lines of the renewable population of genetically diverse individuals comprise less than about 100 strains, in one instance a BXD set of 26 RI lines is used(page 5234). Experiments were also performed using the AXB and BXA RI strains to evaluate both spontaneous and teratogen-induced clefting resulting in both visual and physiological phenotypes. The reference uses the extensive data on teratogen-induced clefting in the AXB and BXA RI lines collected previously with a genome wide collection of marker typings for these RI lines to study the effects of genetic polymorphisms segregating in the renewable population(page 5232, left column). Diehl et al. teach the resulting molecular phenotype of their mouse mutants with clefting phenotypes to include for example, eight collagen genes including an altered expression of one, *Col3a1*, which is normally expressed in the embryonic palate. The reference also teaches the method for identifying multiple genetic loci further comprising identifying two or more genetic loci that modulate the phenotype of clefting as seen on the reference's page 5235 in their explanation that in addition to *Col3a1*, two other genetic factors, *Col1a1* and a cyclic nucleotide phosphodiesterase gene are located on the same chromosome and are thought to together, be possibly relevant to the role of cAMP in the etiology of cleft palate abnormalities(page 5235). Additionally, the reference teaches the implication of the tenascin C gene, an extracellular matrix

protein, and several cell-signaling molecules which have been previously implicated in clefting. Diehl et al. further teach the modulation of the clefting phenotype by a non-genetic factor that is a drug exposure and an interaction between two or more non-genetic factors that are drug exposures. The reference reports the findings of a genome-wide search for susceptibility genes for teratogen-induced clefting in the AXB and BXA set of recombinant inbred mouse strains, as they compare the results and the interaction between phenytoin(which induces cleft lip) and 6-aminonicotitinamide(which indices cleft palate) and the cleft palate phenotype(abstract and page 5231). The reference also teaches the method of a non-genetic factors ability to modulate the clefting phenotype wherein the phenotype is modulated by environmental, non-genetic factors such as a fetus' exposure in utero to ethanol, trimethadione, aminopterin and retinoic acid(page 5231). Included then in these findings are the reference's teachings of the identification of an interaction among two or more non-genetic factors(both environmental and drug-like) and a genetic locus. Furthermore, as stated previously, this same identification was made among multiple genetic loci discovered in this study in addition to those gene mutations that are well known in the art that the present reference reiterates, such as *Msx1*, several *Hox* genes, retinoic acid receptor alpha locus etc,(page 5231).

Diehl et al do not teach the derivation of the RI lines from at least 3, 4 or 8 non-recombinant parent lines.

However, Dindzans et al. teach "the mode of inheritance of susceptibility/resistance to mouse hepatitis strain 3 (MHV)-3 being determined by typing the set of AXB/BXA recombinant inbred (RI) strain derived from **resistant** A/J and **susceptible** C57BL/6J progenitors for susceptibility to infection as determined by the severity of live pathology". "The strain

distribution pattern for susceptibility showed a discontinuous variation: one strain was fully resistant(like A/J), four strains were fully susceptible (like C57BL/6J), and 16 strains showed an intermediate degree of susceptibility"(page 2355). Accordingly, it has been suggested that strain-dependent susceptibility to MHV-3 reflects genetically controlled immune defects rather than differences in the non-genetic, in this case viral factor. It is important to note the need for parental strain diversity that the reference teaches as " the AXB/BXA RI strains used in these experiments were derived from susceptible (C57BL/6J) and resistant (A/J) progenitors representing extremes in disease" for the sole purpose of creating RI strains exhibiting distinct patterns of MHV-3 induced liver pathology, and a discontinuous strain distribution pattern of S/R was seen(page 2357, discussion). This reference then teaches the importance of having an "unique assortment of parental genes that are homozygous at every locus, as such strains are useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control"(page 2355).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the identification of a genetic locus that modulates a phenotype method of Diehl et al. so as to have included the diverse population of non-recombinant, parent lines derived from at least 3, 4, or 8 non-recombinant parent lines for the expected benefit of providing an additional means for furthered variation among mouse lines. Therefore, combining the teachings of Diehl et al. in view of Dindzans et al. would have been obvious at the time the invention was made.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 and 46-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-27 and 46-53 are indefinite over the recitation of "renewable population." It is unclear if the applicant intended for the renewable population to mean: a perpetuated-living cell line, a freezer stock, desiccated sample, etc. Applicant should amend the claims to clarify their intended meaning of "renewable population."

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

2/24/2003

CARLA J. MYERS
PRIMARY EXAMINER